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Modelling mammography screening for breast cancer in the Canadian context: Modification and testing of a microsimulation model

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Abstract

Background: Modelling is a flexible and efficient approach to gaining insight into the trade-offs surrounding a complex process like breast screening, which involves more variables than can be controlled in an experimental study.

Data and methods: The University of Wisconsin Cancer Intervention and Surveillance Modeling Network (CISNET) breast cancer microsimulation model was adapted to simulate breast cancer incidence and screening performance in Canada. The model considered effects of breast density on the sensitivity and specificity of screening. The model's ability to predict age-specific incidence of breast cancer was assessed.

Results: Predictions of age-adjusted incidence over calendar years and age-specific incidence of breast cancer in Canadian women are presented. Based on standard screening strategies, ratios of *in situ* to invasive disease and stage distribution of disease at diagnosis are compared with data from the British Columbia provincial screening program.

Interpretation: The adapted model performs well in predicting age-specific incidence and cross-sectional incidence in the absence of screening. The ratios of detection of *in situ* to invasive cancers and the overall stage distribution of detected cancers are in reasonable agreement with empirical data from British Columbia.

Key words: Breast screening, incidence, microsimulation model, preventive health, sensitivity, specificity

Organized provincial breast cancer screening programs have operated in Canada since 1988. These programs contribute to mortality reduction, but they use substantial resources.

No screening test is perfect; all have limitations. In addition to providing benefits such as reduction of mortality and/or morbidity, they can cause harm, such as biopsies when cancer is not present. Decisions about whether to screen, who should be screened, how frequently to screen, and what modalities to use are best made when the trade-offs between improved health outcomes, potential harms, and monetary costs of the intervention are understood. Modelling offers a flexible and efficient approach to gaining insight into these trade-offs, which involve too many variables to control in an experimental study.

This article describes the modification and testing of a validated microsimulation model of breast cancer, which was developed based on the U.S. population. The modifications reflect the current Canadian context—Canadian-specific data on detection and treatment were incorporated into the model or used as inputs.

Methods

Model

The University of Wisconsin Breast Cancer Epidemiology Simulation Model,[1] developed under the U.S. National Cancer Institute-funded Cancer Intervention and Surveillance Modeling Network (CISNET) program, was used for this study.[2] The model is a "discrete-event simulation model" that reflects U.S. breast cancer incidence and mortality trends from 1975 to 2000 and then extended to 2010. It allows simulation of the growth of a distribution of breast cancers within a cohort of women and consideration of the individual effects of various detection strategies and treatment regimens on mortality and other outcomes. Details about the model[3] are available at: www.cisnet.cancer.gov.

In the model, cancer progression follows a sequence from *in situ* to local invasive cancer to nodal involvement to distant metastasis according to the size and growth rate of the primary tumour. Cancers grow until they are detected because of symptoms or through screening, at which point treatment is initiated. Based on the characteristics of the cancer (size, stage) at the time of detection and the therapy regimen, a woman either survives the disease or dies from breast cancer at a time determined by the growth rate of the tumour (if she has not already died of another cause). The model predicts both *in situ* and invasive cancers. Some *in situ* and early localized cancers are assumed to have "limited malignant potential," and in the absence of screening do not lead to breast cancer death. Because the underlying breast cancer incidence rate has been rising over time, the model incorporates a birth-year dependence on the tumour onset rate.[3,4]

A detection function in the model simulates the screening process. Sensitivity (ratio of screen-detected cancers to the sum of screen-detected plus interval cancers) is determined as a function of tumour size, age group of the woman, breast density,

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and imaging modality. Specificity is determined as a function of age, breast density, and imaging modality. Empirical data on sensitivity are used to calibrate the parameters of the detection function; empirical data on specificity are applied as direct inputs to the model. Symptomatic detection by the woman between screening examinations is also a function of tumour size.

For a specified screening strategy (age of starting, age of stopping, screening interval), including No Screening, the model initially predicts age-specific breast cancer incidence. It also incorporates modules that allow modeling of different treatment regimens and mortality from breast cancer or another cause.

The model is designed to perform calculations for a birth cohort (females born in the same year). This allows estimation of age-specific breast cancer outcomes such as incidence and mortality, independent of cross-sectional population-based effects associated with year of birth. Published data were used to describe the accuracy of cancer detection.[5,6]

Input parameters

The key parameters in the model were adapted to reflect the Canadian experience, including age-specific breast cancer incidence rates and test sensitivities and specificities. To model therapy and outcome, the percentages of women with ER+/ER- (estrogen receptor positive/estrogen receptor negative) disease were assigned by the model based on U.S. SEER data.[7,8] Unlike previous model implementations,[9] HER2/neu status was also assigned to women with cancer. HER2 (human epidermal growth factor receptor 2) is a protein that promotes the growth of cancer cells.

Underlying breast cancer incidence in the absence of screening was modified to predict Canadian incidence data,[10] which are about 15% lower than those for the U.S.

Mammography is not a perfect detection tool. Its sensitivity varies from about 60% to 90%, mainly depending on breast density. Also, some screening mammograms trigger recalls for further non-invasive imaging—typically, a magnification mammogram or breast ultrasound, although an MRI may be requested. In most cases, the additional information reveals that breast cancer is not present. The fraction of women who undergo additional imaging and do not have breast cancer is (1- Sp, or fraction of women recalled in whom cancer was not diagnosed), where Sp is the specificity of screening. Specificity varies from 85% to 96% and is generally lower for the initial screening (when no images from a previous examination are available for comparison) and increases on subsequent examinations. For British Columbia women in their 40s, first-screen specificity is 85.4% and rises to 91.3% on recurring screens.[6] For each screening strategy, the number of recalls for non-invasive imaging that arise from the lifetime screening experience per 1,000 women alive at age 40 and the fraction of women recalled in whom cancer was not diagnosed were calculated.

The sensitivities and specificities for screening mammography were updated based on data from the U.S. National Cancer Institute's Breast Cancer Surveillance Consortium (BCSC),[5] and from the Screening Mammography Program of British Columbia.[6] The BCSC data reflect screening performance as currently used in community settings. Sensitivity and specificity values were stratified by age and breast density. Density was defined using the four American College of Radiology Breast Imaging Reporting and Data System categories: mainly fatty, scattered densities, heterogeneously dense, and extremely dense.[11] The British Columbia data were available at more granular age categories, and both sensitivity and specificity varied approximately linearly over the 40-to-80 age range. Therefore, the data were obtained by interpolating the BCSC sensitivity and specificity data to the midpoint of each age group (Table 1). In the model, women were randomly assigned to one of the four breast density categories, with probabilities following the age-dependent density distributions for Canadian women.[12] Sensitivity and specificity generally increase with decreasing breast density and advancing age. Sensitivity typically increases with time since the previous screen (cancers have had more time to grow); specificity tends to behave in the opposite manner, being highest when screening occurs annually.

The model parameters for detecting very small cancers (considered in the model as *in situ*) were further adjusted to improve the match to the observed ratio of detected *in situ* cancers to invasive cancers reported in the Screening Mammography Program of British Columbia (SMPBC).[6] This adjustment resulted in a 30% reduction for detecting *in situ* tumours. The rationale for the adjustment was that many of these very small (less than 0.5 mm diameter) *in situ* cancers would not be accompanied by microcalcifications (which would greatly increase their contrast on a mammogram) and would, therefore, be occult to mammography. These undetected cancers would remain in the pool until they were large enough to be detected by the woman herself or at a subsequent screening examination.

Outcome measures

For each woman, the model recorded the age at detection of a breast cancer and its "stage" (*in situ*, local invasive, regional involvement, or distant metastasis).

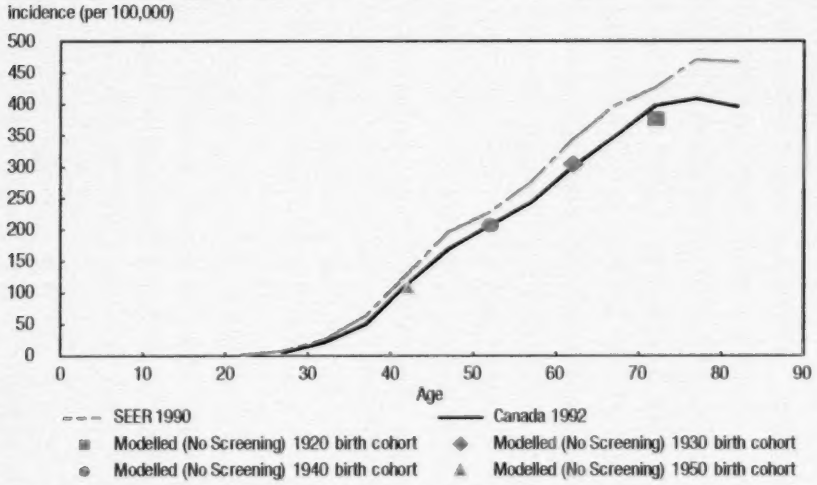
To establish model validity, model-predicted breast cancer incidence was compared with observed Canadian data. For these comparisons, model calculations were performed using multiple birth cohorts to create a cross-sectional representation of the population. Age-specific incidence of invasive breast cancers in the absence of screening was estimated using the model for birth years 1950, 1940, 1930 and 1920. These values were compared with observed cross-sectional incidence data for 1992, as reported by Statistics Canada[10]; this was an era before widespread screening, and a point at which these women would be approximately 40, 50, 60, or 70 years

Table 1
Sensitivity and specificity data used to calibrate model, by screening frequency, breast density and age at exam

	Age at exam							
	40 to 49		50 to 59		60 to 69		70 to 79	
Screening frequency and breast density	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Initial screen								
Extremely dense	0.81	0.82	0.89	0.84	0.91	0.85	0.92	0.87
Heterogeneously dense	0.9	0.78	0.88	0.8	0.91	0.82	0.93	0.83
Scattered	0.92	0.83	0.93	0.84	0.95	0.86	0.96	0.87
Mainly fatty	0.94	0.9	0.86	0.91	0.89	0.92	0.91	0.93
Recurring annual screen								
Extremely dense	0.65	0.9	0.78	0.91	0.81	0.92	0.85	0.93
Heterogeneously dense	0.79	0.87	0.78	0.88	0.81	0.89	0.85	0.91
Scattered	0.85	0.9	0.85	0.91	0.88	0.92	0.91	0.93
Mainly fatty	0.85	0.95	0.73	0.95	0.77	0.96	0.81	0.96
Recurring biennial screen								
Extremely dense	0.73	0.88	0.83	0.9	0.86	0.91	0.89	0.92
Heterogeneously dense	0.84	0.85	0.83	0.87	0.86	0.88	0.89	0.89
Scattered	0.88	0.89	0.89	0.9	0.91	0.91	0.92	0.92
Mainly fatty	0.89	0.94	0.8	0.94	0.83	0.95	0.87	0.95
Recurring triennial screen								
Extremely dense	0.82	0.88	0.85	0.89	0.88	0.9	0.91	0.91
Heterogeneously dense	0.81	0.84	0.84	0.86	0.87	0.87	0.9	0.88
Scattered	0.88	0.88	0.9	0.89	0.92	0.9	0.93	0.91
Mainly fatty	0.78	0.93	0.81	0.94	0.84	0.95	0.87	0.95

Note: Values interpolated from data published by Screening Mammography Program of British Columbia[6] and Breast Cancer Screening Consortium.[5]

Figure 1
Age-specific incidence rate of invasive breast cancer from Surveillance, Epidemiology and End Results (SEER) Program[13] (1990) and Statistics Canada[10] (1992), by age, and modelled incidence rate in absence of screening (1990), by selected birth cohort



Note: The cancer onset rate in the model was decreased by 15% from that used in U.S. studies to better reflect Canadian incidence rates.[10]
Sources: Surveillance, Epidemiology and End Results Program; Canadian Cancer Registry; University of Wisconsin Breast Cancer Epidemiology Simulation Model; Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

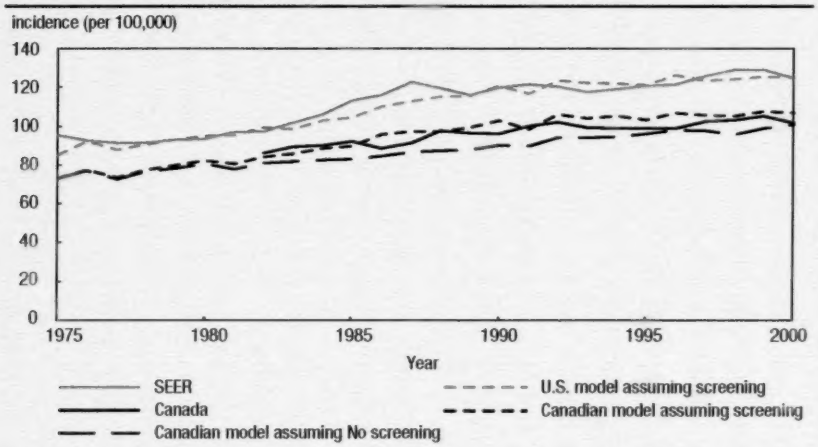
old. The modified model was also run, where multiple weighted birth cohorts were applied to estimate age-adjusted breast cancer incidence. Finally, the predicted *in situ*/invasive cancer detection ratios were compared with data from the SMPBC.

Results

Figure 1 shows the age-specific incidence rate of invasive breast cancer predicted by the model assuming No Screening, compared with invasive cancer incidence from the SEER Registry[13] and from Canada for 1992. The model was run for different birth cohorts, and the markers show where the age of each cohort coincides with the indicated value as the cohort passes through 1990, compared with the 1992 Canadian data, the earliest year for which data were available.

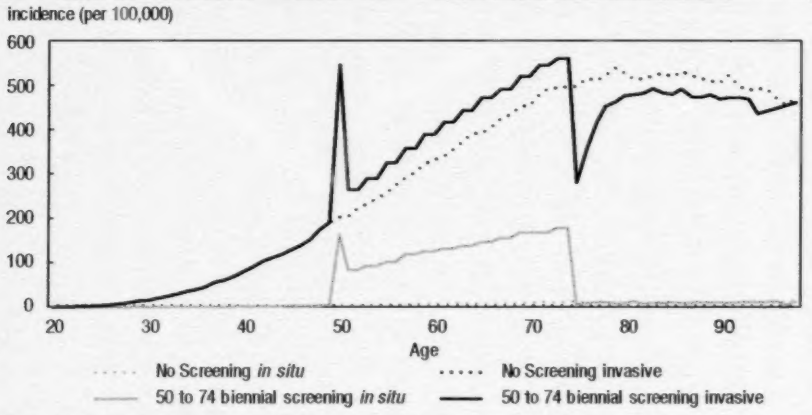
From the model, the lifetime incidence of breast cancer for an unscreened population was calculated as 15%, which

Figure 2
Age-adjusted actual and modelled incidence rate of invasive breast cancer, United States and Canada, 1975 to 2000



Note: Age-adjusted to 1991 Canadian Standard Population from Surveillance, Epidemiology and End Results (SEER) data,[13] using the model for No Screening and U.S. screening patterns and from actual Canadian population incidence data. The cancer onset rate in the model was decreased by 15% from that used in U.S. studies to better reflect Canadian incidence rates.[10]
Sources: Surveillance, Epidemiology and End Results Program; Canadian Cancer Registry; University of Wisconsin Breast Cancer Epidemiology Simulation Model; Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

Figure 3
Model predictions of age-specific incidence rates of invasive and *in situ* breast cancers for No Screening and for biennial screening at ages 50 to 74



Source: Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

Table 2
Detected *in situ*/invasive cancer ratio for model and actual Screening Mammography Program of British Columbia data, by age at exam

Source	Age at exam			
	40 to 49	50 to 59	60 to 69	70 or older
Screening Mammography Program of British Columbia[6]	0.55	0.35	0.28	0.20
Model predictions (annual screening)	0.63	0.62	0.61	0.60
Model predictions (biennial screening)	.	0.32	0.31	0.33

. not available
Note: Values are for all screens except initial screen.
Sources: Screening Mammography Program of British Columbia; Canadianized University of Wisconsin Breast Cancer Epidemiology Simulation Model.

agrees reasonably well with the estimate of 12.6% for the incidence that would currently exist without screening, obtained by extrapolating 1989 incidence to the present at a rate of increase of 1% per year.[11] With annual screening, the predicted lifetime incidence is 19%. The difference reflects the larger number of ductal carcinoma *in situ* predicted to be detected by screening, many of which would be occult in an unscreened population.

Figure 2 gives the incidence rate of invasive cancers for women of all ages, age-adjusted to the 1991 Canadian Standard Population, which was computed using the model. These results can be compared with actual Canadian population incidence data reported by Statistics Canada.[10] In this example, a population approach was taken using an appropriate mix of weighted birth cohorts and U.S. screening dissemination characteristics for the "with screening" curve. Also shown are the SEER data for invasive cancers and results of the U.S. version of the model for the same screening dissemination characteristics.[13] Uptake of screening began later in Canada than in the U.S.

Model predictions of incidence of invasive and *in situ* cancer for both No Screening and biennial screening at ages 50 to 74 are shown in Figure 3. The ratios of detected *in situ* to invasive breast cancer from the model and in SMPBC data are compared in Table 2.

For women aged 50 to 59, the SMPBC reported that approximately 26% of the cancers detected were in situ; 50% were invasive without nodal involvement; and about 15% had progressed to nodal involvement or beyond.[6] The corresponding model predictions for biennial screening in that age range were 25%, 58% and 17%.

Discussion

When the model is applied to the Canadian population, its predictions for invasive cancer agree fairly well with actual Canadian incidence data for 1992 to 2000 (Figure 2). Canadian incidence appears to lie between the model pre-

What is already known on this subject?

- Organized provincial breast cancer screening programs have operated in Canada since 1988.
- Decisions about whether to screen, who should be screened, how frequently to screen, and what modalities to use are best made when trade-offs between improved health outcomes, potential harms, and monetary costs are understood.
- Modelling is a flexible and efficient approach to gaining insight into these trade-offs, which involve too many variables to control in an experimental study.

What does this study add?

- This study describes the modification and testing of a validated microsimulation model of breast cancer, which was developed based on the U.S. population; the modifications reflect the current Canadian context.
- The adapted model performs well in predicting age-specific incidence and cross-sectional incidence in the absence of screening.
- The ratios of detection of *in situ* to invasive cancers and the overall stage distribution of detected cancers are in reasonable agreement with empirical observations.

diction for No Screening and that for observed U.S. screening. All these values are lower than the SEER data.

Breast cancer incidence increased over time. Therefore, year of birth is also a factor in incidence. When the model takes this birth-year dependence into account (for a set of birth cohorts) and is adjusted to use a 15% lower cancer onset than is used in the U.S. for a given calendar year (in this case, 1992), the Canadian incidence data match well with the predicted incidence for a birth cohort that would have reached a specific age that year (Figure 1). Differences between the model and Canadian incidence rates are 3.5%, -0.8%, -1.9% and 5.2% at ages 42, 52, 62 and 72, respectively. The year 1992 was chosen to allow comparison with the model under conditions of No Screening, because almost no organized screening was performed in Canada at that time.

The model predicts that screening yields a modest increase in detection of invasive cancers and a very sharp increase in detection of *in situ* disease (Figure 3). There is reasonable agreement between modelled and observed *in situ*/invasive cancer ratios for annual screening of women aged 40 to 49 and for biennial screening beyond age 50 (Table 2), which was the general practice in British Columbia. The model predicts higher ratios for annual screening in older age groups. It is still possible that detection sensitivity for very small cancers is set too high in the model, a question that will be investigated in future work.

Strengths and limitations

A strength of the model is that the original form was validated against empirical data from the U.S. Modified for use in the Canadian context, it performs quite well in predicting breast cancer incidence in the absence of screening. Also, the model uses recent empirical data on the sensitivity and specificity, which depend on breast density and age and are tabulated as a function of these two variables.

Of necessity, modelling the natural history of breast cancer has limitations. Aside from the application of probabilities for cancers expressing estrogen, progesterone and HER2 neu receptors, no attempt at further characterization (for example, by molecular subtype) was made. The progression from *in situ* to invasive disease was based strictly on the modelled diameter of the tumour, which resulted in some discrepancies between modelled and actual ratios of detected *in situ* to invasive cancers.

Conclusions

The adapted model performs well in predicting age-specific incidence and cross-sectional incidence of breast cancer in the absence of screening. The ratios of detection of *in situ* to invasive cancers and the overall stage distribution of detected cancers are in reasonable agreement with empirical observations from British Columbia. ■

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References

1. Fryback DG, Stout NK, Rosenberg MA, et al. The Wisconsin Breast Cancer Epidemiology Simulation Model. *Journal of the National Cancer Institute Monographs* 2006; 36: 37-47.
2. Feuer EJ, Etzioni R, Cronin KA, Mariotto A. The use of modeling to understand the impact of screening on U.S. mortality: examples from mammography and PSA testing. *Statistical Methods in Medical Research* 2004; 13(6): 421-42.
3. University of Wisconsin. *CISNET Readers Guide*. Core Profile Documentation. Madison, Wisconsin: University of Wisconsin. Available at: https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_BREAST_UWISC_001_07232013_58567.pdf. Accessed: May 1, 2014.
4. Holford TR. Analysing the temporal effects of age, period and cohort. *Statistical Methods in Medical Research* 1992; 1(3): 317-37. Available at: https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_BREAST_UWISC_001_07232013_58567.pdf. Accessed: May 1, 2014.
5. Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms and costs for breast cancer screening following US implementation of digital mammography. *Journal of the National Cancer Institute* 2014; 106(6): dju092 doi: 10.1093/jnci/dju092
6. *Screening Mammography Program 2012 Annual Report*. Available at: http://www.smpbc.ca/NR/rdonlyres/3AF15A7A-B9D4-43C2-A93A-230A634E94AC/60300/SMP_2012AR_WEB.pdf. Accessed: February 26, 2013.
7. Ries LAG, Eisner MP. Cancer of the female breast. In: Ries LAG, Young JL, Keel GE, et al., eds. *Cancer Survival among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics* (NIH Pub. No. 07-6215) Bethesda, Maryland: National Cancer Institute, 2007.
8. Ries LAG, Harkins D, Krapcho M, et al., eds. *SEER Cancer Statistics Review*, 1975-2003. Bethesda, Maryland: National Cancer Institute, 2003. Available at: http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to SEER website, 2006.
9. American Society of Clinical Oncology. *Abstracts for the 2015 ASCO Annual Meeting*. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=49264
10. Statistics Canada. *Table 103-0550 New cases of primary cancer (based on the February 2014 CCR tabulation file), by cancer type, age group and sex, Canada, provinces and territories, annual*. CANSIM (database). Available at: http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1030550. Accessed July 31, 2015.
11. American College of Radiology. *Breast Imaging and Reporting Data System. Fifth Edition*. Reston, Virginia: American College of Radiology, 2004
12. Alonzo-Proulx O, Jong RA, Yaffe MJ. Volumetric breast density characteristics as determined from digital mammograms. *Physics in Medicine and Biology* 2012; 57(22): 7443-57.
13. Surveillance, Epidemiology and End Results Program. *Fast Stats*. Bethesda, Maryland: National Cancer Institute. Available at : http://seer.cancer.gov/faststats/selections.php?series=cancer
14. National Cancer Institute of Canada. *Canadian Cancer Statistics 1989*. Toronto: National Cancer Institute of Canada, 1989.